UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/385,229	02/08/95	JACOBS	C 2503-A

NISBET,J

18M2/1124

IMMUNEX CORP
LEGAL AFFAIRS DEPARTMENT
51 UNIVERSITY STREET
SEATTLE WA 98101

ART UNIT	PAPER NUMBER
1806	21

DATE MAILED: 11/24/95

COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 7/19/95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three month(s), ~~_____~~ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9 are pending in the application.
   Of the above, claims 7 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-6 and 8-9 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

III. DETAILED ACTION

1. Applicant is reminded of the need to update the status of all previous parent applications.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following action on the merits is in response to the amendment filed 7/19/95.

4. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately describe and failing to adequately teach how to make and/or use the instant invention.

The specification recites the following on page 3 at line 14.

> "soluble TNFR molecules include, for example, analogs or subunits of native proteins having at least 20 amino acids and which exhibit at least some biological activity in common with TNFRI, TNFRII, or TNF binding proteins....Equivalent soluble TNFRs include polypeptides which vary from these sequences by one or more substitutions, deletions, or additions and which retain the ability to bind TNF or inhibit TNF signal transduction activity via cell surface bound TNF receptor proteins....".

The specification goes on to refer to proteins having sufficient "homology" without really providing the routineer with an exact definition of how such homology is to be determined. See for example page 6, lines 12 and 30, for example. Without such guidance, undue experimentation would be required to determine which of the substantially "homologous" proteins fall within applicant's disclosure.

Applicants argue that the specification at various positions states that the different mutations and at page 7 provides specific guidance to the routineer to adequately make and use the disclosed invention. Applicants conclude that the specification enables testing with a number of well known methods.

Applicant's arguments have been considered but are not deemed persuasive. The specification does contain specific description of a variety of alterations of the TNFr molecules. However, the description is limited at the C-terminus to deletions to amino acid 142. Therefore, applicants have not teachings concerning the molecule past amino acid 142. Accordingly, a broad reading of the specification disclosed as "variants" or "derivatives" is not supported by sufficient intermediate disclosure to define all derivatives. Therefore, in response to applicant's arguments and the specification at page 7, the disclosure is considered sufficient only for C terminal deletions up to amino acids 142. Likewise, the N terminal alterations of amino terminal

residues Leu, Pro, and Ala is considered sufficient. However, the random alteration of residues between amino acids 3 and 142 is not supported. Moreover conservative substitutions are also not considered enabled without the practice of undue experimentation. Such a conclusion of non-enablement is reached because applicants have not disclosed a discrete assay to which provides an endpoint for the treatment. In other words, in order to test the "variants" or "derivatives" set forth in the specification, some quantifiable assay must be provided to establish functionality. Applicant's arguments that binding is all that is required is not sufficient because binding alone has not been shown to establish *in vivo* functionality. It is noted that the disclosed invention is a method of treatment, not a product which could have *in vitro* assays. Therefore a different kind of endpoint must be established. Moreover, applicant's *in vivo* data is not conclusively correlated with a reduction in disease. If applicants wish to include different TNFr muteins not actually made, then applicants must provide a specific assay which has been correlated with the method of treatment.

In the response filed 7/19/95, applicants argue that at page 3, third paragraph that "the USPTO has erroneously stated that it is the scope of "applicants' disclosure" that is the legal standard. In fact, the scope of applicants's invention is determined by the scope of the *claims* not the scope of their disclosure". While such a statement is well taken, it is noted that the scope of applicants claims recite the use of generic terms such as "TNF receptor" and "chimeric antibody comprising a TNF receptor and the constant domain of an immunoglobulin molecule". These generic terms may be defined by applicant's specification in any way that applicants choose, so long as the lexicography is not repugnant to the art. In the instant case, applicants have chosen to define their proteins in terms that include a variety of different substitutions, deletions and alterations in an area of art which applicants urge is rather unpredictable. Ex parte Hitzeman, 9 USPQ 2nd, 1821, 1822 (Bd. Pat. Appls. and Interf. 1988). In Hitzemann, the Board stated:

> "with respect to the prima facie case of non-enablement, we note that a single embodiment may provide broad enablement in cases involving predictable factors; such as mechanical or electrical elements. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more is required. Id. at 1823.

Therefore, without some specific guidance regarding where the molecule is to be altered and what effect different alterations would be expected to make, undue experimentation would be required to practice the invention as claimed and the rejection is maintained.

The declaration filed with the response of 7/19/95 is considered sufficient to overcome the objection to the claims concerning the statistical significance of the data.

5. Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

6. Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to arthritis. See M.P.E.P. §§ 706.03(n) and 706.03(z).

This is a new grounds of rejection. Base claim 1, and therefore, all claims which depend on claim 1, recite the term "TNF-mediated inflammatory diseases". TNF is a pleiotropic molecule which has many effects. Note the Beutler reference in this regard on the first page of Chapter 1. This term is recited in the specification at pp 15 and 16 where it is listed as arthritic. However, it is noted that the phrase "TNF-dependent inflammatory" diseases encompasses a wide array of diseases such as viral infection, microbial infection, autoimmune disorders, respiratory distress syndrome, and allergies, for example. All these diseases are complex in nature as well as having different pathologies and underlying mechanisms. The current disclosure contains inadequate guidance on how to use the instant TNFr fusion products with any other disease than arthritis. The evidence set forth in the representative examples is limited to arthritis, thus providing no other working examples. Finally, as established in the Steiner reference at the bottom of the right column:

> "The spectacular successes of biotech have mostly been souped-up hormones or enzymes--EPO or Neupogen, Activase, Pulmozyme, or Ceredase-- use in disease precesses where mechanisms of action are straightforward. However, companies that seek to tinker with complex cascades of cytokines, neurotransmitters, parahormones, whatever, have got to be cruising for a bruising."

Consequently, the ordinarily skilled artisan as represented by the Steiner reference clearly considered the art in 1994 (two years post priority) to be unpredictable. Consequently, the exemplification of a single TNF mediated disease without any further guidance would not enable <u>all</u> TNF mediated diseases in the absence of other working examples without the practice of undue experimentation. Therefore, applicant's claims should be limited to the treatment of arthritis.

7. The rejection under § 102 is withdrawn in view of applicant's amendment of the claims to remove the phrase "TNF binding protein". Therefore, the disclosure of Brennan is no longer anticipatory.

8. Claims 1-5 and 8-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Brennan in view of Harris and Smith.

The claims recite the following limitations.

> A method of treating TNF mediated arthritis with a TNFr.

The Brennan reference teaches the inhibition of IL1 production in explanted synovial cell cultures from arthritic human patients. The reduction in the production of IL1 is consistent with the reduction in bone damage and cartilidge destruction associated with rheumatoid arthritis. Note that the reference teaches on pg. 244 first paragraph, "...intra-articular IL1 can induce arthritis.". Therefore, since the source of the synovial cell culture is the human patient, the reference anticipates the rejected claims.

The reference is used as a teaching of expectation of the success because the reference explicitly states that IL1 can induce arthritis and that TNF α inhibitors can reduce the production of IL1. The Brennan reference does not teach the use of TNF receptors. However, this is not considered significant because the TNF receptors of the instant claims and anti-TNF antibodies of Brennan operate by the same mechanism. That mechanism is the binding of TNF so that the TNF molecule cannot interact with other receptors, etc.. Therefore, one of ordinary skill in the art would have known that as long as TNF is removed from the environment, the condition of rheumatoid patients would improve.

The Harris reference teaches the use of cytokine inhibitors for the treatment of rheumatoid arthritis on page 1286, end of the 5^{the} paragraph. Therefore, this reference is sufficient to provide the motivation to use the cytokine inhibitors of the instant invention.

The Smith reference provides the sequence of the p80TNFr which was used by applicants in the instant application. The use of such a receptor in the claimed method would have been obvious in view of the cited art set forth above.

The combination of the TNFr of Smith in the methods of therapy set forth in Harris and Brennan references would have been obvious to one of ordinary skill in the art absent evidence to the contrary. The reason for such a conclusion stems from the following disclosures. Because the prior art teaches that an antagonist to TNF will prevent the cause of arthritis (Brennan) and the art recognizes that the claimed compounds were an alternative antagonist to the antibodies of Brennan (see Harris), the routineer would merely substitute the TNFr of Smith for the antibodies of Brennan as taught by Harris to obtain the claimed invention. Therefore, applicant's claimed invention is clearly prima facie obvious absent evidence to the contrary.

The last two claims recite specific dosage amounts and times. However, the dosages are so broad as to represent merely upper and lower extremes. In other words, given the fact that the claimed dose appears to be almost 20 times as strong as that used in the representative examples, the claimed doses are probably toxic. Therefore, absent some clinical significance they are deemed to be obvious in view of the art.

Applicants respond in the 5/5/94 that the Harris and Smith references are not available as prior art. Applicants are not, however, entitled to priority necessary to enable the invention any earlier than the instant filing date. While applicants did disclose the combination of TNF inhibitors with antibody F_c in previous applications, this disclosure was only in general terms and did not contain any detailed **enabling** disclosure which would teach the routineer how to make and/or use the instant invention. The previous disclosures, 07/523,635 for example, contain no evidence to enable the broad assertions of enablement regarding *in vivo* claims. While it is noted that broad assertions of enablemnent can sometimes be sufficient, that no specific requirements exist that a specification contain actual representative examples, and that statements in applicant's specification are presumed to be correct, priority to the parent applications for methods of therapy is not granted for the following reasons. First, no representative examples of the therapy exist. Indeed, even the instant specification contains data which is simply not conclusive of actual disease treatment. Additionally, applicants are dealing in an area of research which is extremely unpredictable. Note the finding of *Hitzemann*, above. Moreover, the state of the art as cited in the previous office action mailed 8/9/94 at the bottom of page 5 establishes that the art of "TNF mediated inflammatory diseases" (scope of claim 1) was "poorly understood". Finally, the nature of the invention is such that cytokine cascades are complex and interdependent. This means that affecting a single member of the cytokine family (TNFα in the instant case) will have a ripple effect throughout the entire *in vivo* system. While any one of the foregoing factors may not be sufficient for a finding of non-enablement, all these factors establish an analysis as set forth in *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. Appls. and Interf. 1986) and applicant's disclosure in their previous parent applications is not considered to be enabling within the meaning of § 112, first paragraph. Accordingly, the rejection is maintained for reasons of record and applicants are not entitled to the priority date of anything earlier than the instant filing.

In the response filed 7/19/95, applicants urge that even if the cited art were valid prior art, the rejection set forth above is merely obvious to try, rather than obvious to succeed. Such arguments are rebutted by the Brennan reference. The Brennan reference essentially copies the instant invention with a different molecule. The molecule is one that binds TNFα. In the case of Brennan, that molecule happens to be an antibody while the newly amended claims recite the addition of a TNFr (receptor) to the chimeric antibody of claim 1. Therefore, the claims still retain the use of an antibody-TNFr fusion product through use of the term "comprising". In other words, the scope of the claim still reads on the use of an entire antibody in addition to a TNF receptor. So, art related to antibody mediated TNFα mediated rheumatoid arthritis is still relevant to the invention as claimed.

Moreover, even if applicants were to limit their claims to TNFr-F_c fusion proteins, the disclosure of Smith *et al* at page 1019, bridging columns states that "clinical interest has focused on TNF because it appears to be a common mediator of inflammation, endotoxin induced shock, ..and neoplastic disease. TNF receptors appear on virtually all somatic cells, and generally the ligands cross-compete for binding...". Therefore, Smith teach that the receptor proteins bind to TNF *in vivo* and that such effects has generated clinical interest. Therefore, given that the antibodies of Brennan function in the same manner as the TNFr. Accordingly, Brennan is sufficient to provide a reasonable expectation of successfully treating a TNF inflammatory disease with the TNFrs of Smith. Accordingly, the rejection is maintained.

9. Claim 6 is rejected under 35 U.S.C. § 103 as being unpatentable over Brennan in view of Harris ,Capon ,and Hoogenboom further in view of Smith.

The rejected claim recites the use of a fusion F_c region with the TNFr protein.

The Brennan, Harris, and Smith references have been discussed above.

The Capon and Hoogenboom references are added to render the addition of the F_c region to the cytokine receptor (TNFr)obvious. The Capon reference teaches generically, the addition of various receptors and soluble derivatives of these receptors to N-terminus of the F_c region. Moreover, the Capon reference teaches the advantages of using such things in the addition of F_c regions for drugs which interrupt ligand and binding partner interactions. See col 4, lines 16 and following. This is exactly what applicants are claiming. The claimed TNFr is a binding partner that is used to antagonize the interaction TNF (ligand) and the cell bound receptor (binding partner). The patent teaches that the addition of the F_c region increases serum half life (see line 40 of col. 4). The Capon reference does not explicitly mention cytokines. That is why the Hoogenboom reference has been used. The Hoogenboom reference teaches the fusion of the TNFr ligand (TNF) to an immunoglobulin F_c region. Therefore, all one of ordinary skill would have to do is substitute the binding partner for the ligand as explicitly recommended by Capon. Accordingly, because Capon teaches the fusion of F_c with ligand antagonists (binding partners) and the Hoogenboom reference teaches the use of such fusions with the TNF/TNFr ligand/antagonist (binding partner) pair, it would have been obvious to one of ordinary skill in the art to perform the fusions of Capon and Hoogenboom on the molecules of Smith with the methods of Brennan and Harris.

Applicants argue in the response filed 7/19/95 that the Capon reference fails to disclose the specific fusion of a TNF receptor to the F_c immunoglobulin domain. Further, Capon is argued not to disclose the use of the TNF fusions in inflammation. In response, the Hoogenboom reference states on page 1027, right col., last paragraph,

that TNF is a mediator of inflammation. Therefore, the prior art specifically teaches the use of the TNF binding protein fusion proteins for use in treating inflammation. In so far as the Capon reference is concerned. Applicant's attention is directed to col. 2, lines 10 and following, for example. The reference teaches the use of many different hormones and growth factors. In short, the reference provides teaching of a wide variety of different receptors. Moreover, claim 2 is generic in claiming a variety of different receptors which generically include the instant TNF antagonists. Accordingly, the claim itself is presumed valid for the scope and therefore, absent unexpected results applicants species is considered to be taught by the generic disclosure of Capon.

Traversal continues with the assertion that the Hoogenboom reference is limited to a anti-transferrin receptor antibody. However, this argument fails to account for the fact that the claims are not limited to any particular antibody constant domain. Second, with respect to the argument that Hoogenboom does not teach fusion of the TNFr to an F_c region. Applicant's attention is directed to page 1029 of Hoogenboom where the reference teaches the production of two chimeric antibody-TNF genes, one with the F_c portion and one without. See the right col., 5 lines from the bottom. It is reiterated that one of ordinary skill in the art would be motivated to substitute the TNF receptor for the TNF in Hoogenboom based on the suggestion in Smith cited *supra*, concerning the clinical interest that has been generated in TNFr and the ability of TNFr to bind to TNF. Consequently, the success enjoyed by Brennan with the TNFrs of Smith in view of the explicit motivation to use cytokine inhibitors in treating arthritis clearly would have rendered the claimed invention *prima facie* obvious at the time the application was filed.

10. The oath is defective in the recitation of the prior application number 07/403,421 as being filed in 1985. The application was filed in 1989. A new oath is required to correct the defect. In the response filed 7/19/95, applicants has not responded to this defect in the oath. Accordingly, it is maintained.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Nisbet whose telephone number is (703) 308-4204 from 9:00 am to 5:00 pm weekdays with the exception of alternating Mondays. If the examiner cannot be reached, the supervisor, Marion Knode, may be contacted at phone number (703)308-4311.

The number for facsimile submission of papers has changed. The new fax number for Art Unit 1806 is (703) 305-7401. Please provide the serial number, application title, examiner's name, and art unit on the fax cover sheet to expedite

clerical processing. In addition, all cover sheets should be marked **DRAFT** or **OFFICIAL** as appropriate.

Any informal communications of a **nonconfidential** nature can be communicated to Examiner Nisbet electronically at the following address, tnisbet@uspto.gov.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TMN
November 13, 1995

PAULA K. HUTZELL
PRIMARY EXAMINER
GROUP 1800